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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,097	WELLSTEIN, ANTON	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *1-9,18-20 and 24-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-17 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-68* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 June 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 10-17 and 21-23) in the Response filed 2 February 2004 is acknowledged. The traversal is on the ground(s) that: **(a)** no serious search burden has been established, **(b)** a search of all the claims would amount to a search of the same subject area, **(c)** no explanation of why it is a serious search burden was presented, and **(d)** most groups fall into one class.

2. This is not found persuasive because as set forth in the previous Office Action (19 August 2003), each of the 10 Groups constitutes an independent and distinct invention without co-extensive searches. Furthermore, the all of the groups do not fall into the same class and subclass, therefore they do not share the same search field. Restriction was deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Inventions IX and X are directed to methods that are distinct both physically and functionally, and are not required one for the other. Invention IX requires search and consideration of evaluating an activity of a substance, which is not required by Invention X. Invention X requires search and consideration of using a protein as a therapeutic agent, which is not required by Invention IX. And Inventions I, II, III, IV, V, VI, VII, and VIII are directed to products that are distinct both physically and functionally, are not required one for the other, and are therefore patentably distinct. Although the isolated polypeptide complex of Invention I can be assembled from the recombinant polypeptides of Invention II and Invention IV, or recombinantly expressed using the nucleic acids of Invention III and V, or purified from natural sources using the antibodies of Invention VI and VII, or the kit of Invention VIII it can be made

through materially different methods such as chemical synthesis. Therefore to search and examine all 10 Groups would present an undue burden on the Examiner as presented in the previous Office Action (19 August 2003).

3. It is noted that in the Restriction Requirement (19 August 2003) the Examiner required restriction between product and method claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn method claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Method claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

4. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined method claims will be withdrawn, and the rejoined method claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and method claims may be maintained. Withdrawn method claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the

method claims should be amended during prosecution either to maintain dependency on the method claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

5. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the Examiner before the patent issues. See MPEP § 804.01. Claims **1-9, 18-20, 24-68** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Response filed 2 February 2004. The requirement is still deemed proper and is therefore made FINAL.

Drawings

6. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: Figure 7C-E, 8A-C, and 9B contain reference symbols which are not defined and are not included in the Specification. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

7. Claim **23** is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the

claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 23 broadens the parent claim to include peptido-mimetics, structures outside the genus of polypeptides.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims **10-17** and **21-23** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *the recombinant human pleiotrophin receptor protein ALK comprising one or more but not all regions selected from the group consisting of an extracellular domain (ECD), an intracellular domain (ICD), a pleiotrophin binding site, a transmembrane domain, and combinations thereof as well as compositions thereof*, does not reasonably provide enablement for *other variants, fragments, domains, or peptido-mimetics as well as compositions thereof*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

9. The claims are drawn very broadly to any pleiotrophin receptor protein lacking a region or domain. The language of said claims encompasses all species of pleiotrophin receptor as well as unknown or as of yet identified pleiotrophin receptors.

10. The Specification teaches that the human pleiotrophin receptor (ALK) is composed of three principal regions, an extracellular domain (ECD), a transmembrane region (TM), and an

intracellular domain (ICD) (Figure 1A). ALK binds pleiotrophin (PTN) and functions in tumor growth, endothelial cell growth, neural cell growth, activation of Ras-related activities, cellular invasion (motogenic activities), metastasis, angiogenic activities, and developmental regulation (pp. 9-10). The Specification also teaches that the pleiotrophin binding domain lies within residues 368-447 of the human pleiotrophin receptor protein (pp. 14).

11. However, the specification fails to provide any guidance for the successful isolation and characterization of all species of pleiotrophin receptor and other domains besides extracellular domain (ECD), an intracellular domain (ICD), a pleiotrophin binding site, a transmembrane domain or peptido-mimetics. And since resolution of the various complications in regards to targeting a domain in a protein is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with known domains as to ascertain their identity. In the absence of any guidance from the specification, the amount of experimentation would be undue, as the claims as currently presented represent an invitation to experiment, first to identify, then characterize, and then manufacture the desired mutants. Thus one would have been unable to practice the invention over the scope claimed.

12. Additionally, a person skilled in the art would recognize that predicting the identity and function of domains of any given pleiotrophin receptor protein based solely on a single species of pleiotrophin receptor as highly problematic (see MPEP §2164.03). Thus, although the specification prophetically considers and discloses general methodologies of identifying said

domains (or regions), such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

13. The following references are cited herein to illustrate the state of the art of pleiotrophin and protein biochemistry.

14. On the state of the prior art, Meng *et al.* (14 March 2000) "Pleiotrophin signals increased tyrosine phosphorylation of β-catenin through inactivation of the intrinsic catalytic activity of the receptor-type protein tyrosine phosphatase β/ζ." PNAS **97**(6): 2603-2608 teaches that pleiotrophin (PTN) binds to the receptor protein tyrosine phosphatase (RPTP) β/ζ (pp. 2603; Figure 2). Meng *et al.* teaches that the family of RPTPs are single-chain transmembrane proteins with either one or two intracellular tyrosine phosphatase domains, single transmembrane domains, and variable extracellular domains (pp. 2607). However, Meng *et al.* does not teach which domains are sufficient and necessary to bind PTN, or which residues are important to maintain the biological activity. Thus the skilled artisan is not offered any support to make or use

the invention as claimed which requires the deletion of at least one domain while still remaining a PTN binding receptor.

15. Regarding derivatives and fragments of pleiotrophin receptor polypeptides, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the

current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

16. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *prophetic suggestion* to identification, characterization, and isolation of the full scope of pleiotrophin receptor protein mutants as exemplified in the references herein.

17. Claims **10-17** and **21-23** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

18. The claims require "a growth factor binding site, a mitogenic factor binding site, an antigenic domain, tyrosine kinase, a heparin binding site, a glycosylated domain, a non-glycosylated domain, a signaling domain, a functional domain, and a conserved domain" but do not require that the domains to possess any particular conserved structure, or other distinguishing feature nor does the Specification delineate their position (via residues numbers) in any given pleiotrophin receptor protein. Thus, the claims are drawn to a genus of domains that are defined by hypothesized function and unknown location.

19. The claims require antigenicity, anti-angiogenic activity, pro-apoptotic activity, anti-motogenic activity, anti-mitogenic activity, and anti-cell proliferative activity but do not disclose or require any set structure to possess these biological activities. Thus, the claims are drawn to a genus of domains that are defined by hypothesized function and unknown location.

20. Furthermore the art recognizes that "peptido-mimetic" can pertain to chemical entities, peptides, non-peptide compounds, animal tissue extracts, antibody fragments, cyclic peptides,

agonists, antagonists, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. The claims do not require that the peptido-mimetic possess any particular conserved structure, or other distinguishing feature nor does the Specification delineate a peptido-mimetic of any given pleiotrophin receptor protein. Thus, the claims are drawn to a genus of domains that are defined by hypothesized function and unknown location.

21. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of hypothesized structures. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

22. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed

invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

23. The Examiner notes that a sequence described only by a functional characteristic without any known or disclosed correlation between that function and the structure of the sequence, is not a sufficient identifying characteristic to satisfy the written description requirement. The instant claims present such an instance where Applicant has only described what is desired but does not evidence material possession of the invention at the time of filing through means of sequence disclosure or detailing of its structure {see MPEP §2163 I(A)}.

24. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of the enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled

in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

25. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

26. Claims **10, 11, 12,** and **21** are rejected under 35 U.S.C. 102(b) as being anticipated by Maeda *et al.* (30 April 1999) "A Receptor-like Protein-tyrosine Phosphatase PTPξ/RPTPβ Binds a Heparin-binding Growth Factor Midkine." The Journal of Biological Chemistry **274**(18): 12474-12479.

27. Claims 10 and 11 require a recombinant pleiotrophin receptor protein comprising one or more but not all regions including but not limited to extracellular domain (also known as a region in the art). This claim language broadly encompasses any receptor protein which binds

pleiotrophin and lacks a domain or region. Claim 12 recites that the polypeptide is antigenic, an inherent property of proteins. Claim 21 requires a composition of said pleiotrophin receptor protein, no specific ingredients are delineated.

Maeda *et al.* teaches PTPξ/RTPβ (PTPξ) is a receptor-like protein-tyrosine phosphatase which binds pleiotrophin. Maeda *et al.* teaches that are three splice variants of PTPξ: the full-length PTPξ (PTPξ-A), the short form of PTPξ in which most of the serine, glycine-rich region is deleted (PTPξ-B), and the secreted form, PTPξ-C, which corresponds to the extracellular region (domain) of PTPξ-A thus meeting the limitations of claims 10 and 11 (pp. 12474-12475; Figure 2). The Examiner notes that polypeptides are by definition antigenic, as amino acid sequences routinely comprise epitopes. Since a compound and all of its properties are inseparable, the polypeptide as taught by Maeda *et al.* inherently meets the limitations of claim 12 (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)).

28. Maeda *et al.* teaches the dilution of PTPξ in 0.5% BSA, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 0.1% CHAPS, 0.15 M NaCl, 10 mM sodium phosphate, at pH=7.2 thus meeting the limitations of claim 21 (pp. 12475).

Summary

29. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
April 21, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER